

Inamed
CosmoDerm™ Human-Based Collagen Implant

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION:

CosmoDerm collagen implants are sterile devices composed of highly purified human-based collagen that is dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine. CosmoDerm collagen implants are available in two forms: CosmoDerm 1 collagen implant and CosmoDerm 2 collagen implant. CosmoDerm 2 collagen implant contains almost twice the collagen concentration of CosmoDerm 1 collagen implant.

CosmoDerm 1 and CosmoDerm 2 contain collagen purified from human fibroblast cell culture. The cell line used for collagen production is qualified by extensive testing for viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity. Prior to release each lot of human collagen is tested for protein concentration, purity, pH, lidocaine content, residue on ignition, differential scanning calorimetry, extrusion, appearance, sterility and pyrogenicity.

2. INTENDED USE / INDICATIONS

CosmoDerm collagen implants are injected into the superficial papillary dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

3. CONTRAINDICATIONS

- CosmoDerm collagen implants must not be used in patients with severe allergies manifested by a history of anaphylaxis.
- CosmoDerm collagen implants contain lidocaine and must not be used in patients with known lidocaine hypersensitivity.
- CosmoDerm collagen implants are contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

4. WARNINGS:

- CosmoDerm collagen implants must not be implanted into blood vessels. Avoid forceful injection into superficial dermal arterial branches of the face and scalp that could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Implantation of CosmoDerm collagen implants into dermal vessels may also cause vascular occlusion, infarction, or embolic phenomena, because collagen can initiate platelet aggregation.

- Local necrosis is a rare event, which has been observed following bovine collagen implantation. Most necroses reported through post-marketing surveillance of bovine dermal collagen have occurred after injection into the glabella.
- Some physicians have reported the occurrence of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), and dermatomyositis (DM) subsequent to bovine collagen injections in patients with no previous history of these disorders. Conflicting studies have been published in peer reviewed journals regarding the association between PM/DM and injectable bovine collagen. A causal relationship between bovine collagen injections and the onset of PM/DM, or the other connective tissue diseases listed, has not been established. The incidence and severity of such reactions after human collagen injections has not been determined.
- An increased incidence of cell-mediated and humoral immunity to various collagens has been found in systemic connective tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. The incidence and severity of such reactions with human collagen injections has not been determined. Therefore, caution should be used when treating these patients.

5. PRECAUTIONS:

- CosmoDerm collagen implants are packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on experience with bovine collagen implants, the use of CosmoDerm 1 collagen implant in an individual patient should be limited to 30 ml over a one-year period. Use of CosmoDerm 2 collagen implant in an individual patient should be limited to 15 ml over a one-year period. The combination of these products or of CosmoDerm in conjunction with CosmoPlast collagen implant in an individual patient should be limited to 30 ml over a one-year period. The safety of injecting greater amounts on an annual basis has not been established.
- The safety of CosmoDerm use in patients with a known hypersensitivity to bovine collagen has not been studied.
- Injectable collagen should be used with caution in patients who are atopic or have a history of multiple allergies. Such patients may have a greater potential for exhibiting an allergic reaction.
- As with all transcutaneous procedures, CosmoDerm collagen implantation carries a risk of infection.

- Use of CosmoDerm collagen implants at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present, should be deferred until the underlying process has been controlled.
- The safety of CosmoDerm collagen implants for use during pregnancy or in infants and children has not been studied.
- CosmoDerm collagen implants should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- Based on experience with bovine collagen implants, CosmoDerm overcorrection of the periorbital area and vermilion border of the lip may be slow to resolve due to minimal tissue stresses at these sites. Therefore, caution is advised when overcorrecting these areas of the face. Special caution should be used when implanting CosmoDerm 2 collagen implant at these sites, because the more concentrated material may result in an even slower resolution of the overcorrection.
- The safety and effectiveness of CosmoDerm implantation for use in lip augmentation has not been established.

6. ADVERSE EVENTS

A. Human Collagen Implants

In a study to evaluate sensitization to CosmoDerm and CosmoPlast, 428 patients were injected intradermally with CosmoDerm 1 into the volar forearm and followed for 2 months. All reported adverse events with two or more occurrences in this study, are listed in Table 1 in descending order according to frequency.

Table 1 - Adverse Events with Two or More Occurrences in the Sensitization Study

Description of Adverse Event	Number	% Frequency
Cold Symptoms	17	4.1
Flu-Like Symptoms	8	2.0
Urinary Tract Infection	4	1.0
Bronchitis	3	0.7
Strep Throat	3	0.7
Sinus Infection	3	0.7
Acid Dyspepsia or Reflux	2	0.5
Back Ache, Pain, Spasm	2	0.5

Description of Adverse Event	Number	% Frequency
Ear Infection	2	0.5
Fever and Slight Fever	2	0.5
High Blood Pressure	2	0.5
Insomnia	2	0.5
Sore Throat	2	0.5

Local Treatment Site Reactions

One subject reported redness and pain (moderate severity) at one week after the first injection. This was confirmed by the investigator as redness, tenderness, induration and swelling at the injection site. These symptoms spontaneously resolved after 10 days without treatment or sequelae. The absence of an antibody response against CosmoDerm and histopathological examination of a biopsy of the injection site suggested that the injection site reaction was not immunologically-related to CosmoDerm injection.

B. Bovine Collagen Implants

The following adverse event information on Zyderm and Zyplast bovine collagen implants is based on a clinical study of 2800 Zyderm patients between 1979 and 1981, and 559 Zyplast patients between 1982 and 1986, as well as on post-market reports.

Sensitization reactions to injectable bovine collagen implants have occurred in 1-2% of treated patients, and have consisted of erythema, swelling, induration and/or urticaria at implantation sites. Often these reactions have occurred following an unrecognized or unreported positive bovine collagen skin test. Most of the remaining responses occurred in patients who became sensitized to Zyderm bovine collagen implant at some point during their course of treatment. Approximately 80% of these reactions occur within four weeks following the sensitizing dose.

Typically, allergic reactions to bovine collagen persist between one and nine months, with an average duration of four months. These reactions may be intermittent or continuous in nature. In rare instances, reactions have resolved in one or two weeks or have persisted for more than one year. Although several forms of therapy (antihistamines, NSAIDS, oral, topical and intralesional steroids) have been tried, they usually resulted in only temporary improvement. In most cases, time has proven to be the determining factor in the resolution of these reactions. In rare instances, patients have been left with residual firmness at the site of a resolved adverse reaction.

On rare occasions, the hypersensitivity response has progressed to a cystic reaction that may drain purulent material. The incidence and severity of this type of hypersensitivity response reported to date has been greater with Zyplast bovine collagen implant than with Zyderm bovine collagen implant. These reactions develop weeks to months following injection, may result in scar formation, and rarely require medical revision to correct. This type of reaction can occur as multiple and/or recurrent sterile abscesses, which tend

to be persistent and resistant to drug therapy; careful incision and drainage has been a useful treatment.

Infections at implantation sites have occurred in less than one per thousand bovine collagen treated patients, and herpes simplex eruptions at sites that had been previously affected with herpes simplex, have been reported in less than one per ten thousand patients. These responses typically resolved quickly and without sequelae.

Systemic complaints have been reported by less than 0.5% of bovine collagen implant patients. During clinical testing and subsequent monitoring of patient complaints following exposure to Zyderm bovine collagen implant, a variety of systemic complaints has been reported. These reports have included flu-like symptoms (fever, myalgia, neuralgia, headache, nausea, malaise, or dizziness); pruritis; rash; transient visual disturbances including blurred vision; tingling and numbness; transient polyarthralgia; and various systemic diseases including immune-mediated diseases. Rare anaphylactoid responses have been reported with Zyderm bovine collagen implant, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

As with any injection into the head or neck, the injected material may be inadvertently implanted in a blood vessel. Localized necrosis and/or sloughing, resulting in a scab and/or a scar, may occur following interruption of blood flow through blood vessel laceration or occlusion, or through tissue overdilatation that compromised vascularity. The extent of necrosis varies and follows the pattern of the tissue served by the vessel involved. This phenomenon has been reported more frequently in the glabellar region of the face than in other areas; nevertheless, the incidence with bovine dermal collagen is less than 1% of treated patients. Scar formation may also occur in conjunction with either infection and/or hypersensitivity responses. If implantation is followed by prolonged blanching or significant ecchymosis at the treatment site, gentle massage and close follow-up are recommended.

Forceful injection into superficial dermal arterial branches of the face and scalp could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Such a complication, although unlikely, has been reported with the use of Zyderm collagen implant in one patient, and resulted in the sudden and permanent loss of vision in one eye. Similar complications have been associated with other injectable preparations, including corticosteroids, local anesthetics, and angiographic agents. These findings emphasize the importance of avoiding implantation into blood vessels.

Local Treatment Site Reactions

Transient or minimal swelling, mild redness, and discomfort will probably occur at the implant site immediately following implantation. Increasing discomfort or swelling, or spreading redness should immediately be brought to the physician's attention.

Transient pain and tenderness at injection sites has been associated with the injection of collagen implants. On occasion, transient painless bruising or discoloration has been noted to develop at one or more of the implantation sites. Resolution has usually been spontaneous.

Less than 1% of patients receiving Zyderm bovine collagen implant have at some time reported an intermittent swelling response, involving moderate induration at the implant site and edema within the surrounding tissues. In some cases, these responses have been found to be associated with antibodies to bovine collagen. At times this has been accompanied by mild pruritis or minimal erythema, which may persist for a period up to several months. These reactions may last only a few hours and are usually associated with causes of peripheral vasodilatation, such as consumption of alcohol, prolonged exposure to sun and/or heat, exercise, and flare-ups of hay fever and other causes of nasal and sinus congestion. To date, these reactions have been self-limiting and have not been shown to adversely affect the long-term success of collagen implant correction; although, they may persist throughout the life of the implant.

Infections and reactivation of a pre-existing herpes simplex infection at collagen implant sites may occur in treated patients.

Approximately 20% of patients treated with Zyderm 2 bovine collagen implant have reported temporary palpable lumpiness or visible white patches at injection sites. Both of these types of treatment-associated responses resolved spontaneously without sequelae, and are believed to reflect the fact that with Zyderm 2 bovine collagen implant, a higher concentration of collagen can be injected in a single treatment session.

7. CLINICAL STUDIES:

A. Human Collagen Implants

Study Design:

A prospective, open label clinical study was conducted to evaluate patient immune system responses to CosmoDerm. Male and female subjects who were 18 years of age or older were enrolled. Exclusion criteria were: pregnant and/or nursing, treated with chemotherapy agents or corticosteroids within the past 3 months, allergic to lidocaine, or currently receiving treatment with immunosuppressive drugs. Patients were also excluded if they had a history of an autoimmune disorder, severe allergies manifested by a history of anaphylaxis, or a current disease state that could affect an immune response (e.g., flu, cancer, HIV).

A pre-treatment blood sample was taken followed by a 0.1 ml intradermal injection of CosmoDerm 1 into the volar forearm. The test site was monitored daily by the subject for signs of systemic and local reactions (e.g., erythema, pain, swelling). Each subject returned to the clinic at approximately 72 hours after the first CosmoDerm injection to have any observations recorded. After a 30-day observation period, subjects returned to the clinic for a second CosmoDerm injection, and the same procedures of test site observation by the

subject and a 72-hour visit with the clinical staff took place. Thirty days after the second CosmoDerm injection, subjects returned for a final clinic visit, which included a post-treatment blood draw.

CosmoDerm Immune Response

Serum samples obtained before CosmoDerm exposure and 30 days after the second CosmoDerm injection were assessed with an ELISA capable of detecting IgG, IgM and IgA antibodies against Type I human collagen. No positive responses against human Type I collagen were observed. Equivocal titers (titers of 40-80), were found in four samples. Two of these four samples were from the same subject who displayed a pretreatment titer of 40 and post-treatment titer of 80. Of the remaining two equivocal samples, one subject's sample (with a titer of 40) was pre-treatment, and a negative result was observed post-treatment. The other equivocal response (with a titer of 40) was from a post-treatment sample of a different subject. None of the equivocal response serum samples cross-reacted with bovine collagen.

B. Bovine Collagen Implants

Zyderm was studied in approximately 2800 patients with soft tissue contour deficiencies, most of which were treated between 1979 and 1981 by 400 investigators. While acne was treated in approximately 50% of the patients, a variety of soft tissue contour deficiencies were treated. Facial lesions accounted for approximately 95% of the soft tissue contour deficiencies. A random sample of 95 patients was asked to provide a self assessment of the percent of correction at up to six months after their last treatment. Forty-seven patients responded and reported a median correction of 60-79%.

8. INDIVIDUALIZATION OF TREATMENT:

Severely indurated, sharply marginated and very superficial lesions (e.g., ice-pick acne scars, viral pockmarks, and superficial rhytides such as some perioral lines) may be difficult to distend and, therefore, difficult to correct. If a defect cannot be distended because of extensive scarring or non-elastic tissue, the course of correction will be prolonged, if correction is achievable.

Based on post-marketing studies with Zyderm bovine collagen, touch-up implantations at 6-18 month intervals may be required to maintain maximum correction. While areas with greater motion or mechanical stress (e.g., nasolabial folds), may require more frequent treatments, lesions such as acne scars may need touch-up injections less frequently. Nevertheless, if a stable level of correction is desired, all patients should be counseled to anticipate supplemental implantations.

9. HOW SUPPLIED

CosmoDerm 1 and CosmoDerm 2 collagen implants are supplied in individual treatment syringes with needles, and are packaged sterile for single patient use, ready for implantation.

To place an order, phone toll-free: (800) 624-4261

INSTRUCTIONS FOR USE:

1. Prior to treatment with CosmoDerm collagen implants, the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to maintain maximum correction.
2. A complete medical history should be obtained to determine whether the patient is an appropriate candidate for CosmoDerm collagen treatment.
3. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pretreatment photographs are recommended.
4. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic.
5. CosmoDerm collagen implants are implanted intradermally through a fine-gauge needle into the plane(s) of apparent deformity. The needle should be placed as superficially as possible in the papillary dermis and the lesion should be deliberately overcorrected. When using CosmoDerm 1 collagen implant, it is recommended that the lesion be over-corrected to 1.5-2.0 times the initial depth of deformity. A lesser degree of over-correction is required to achieve a comparable level of correction when using the more concentrated CosmoDerm 2 collagen implant. If blanching is not achieved, withdraw the needle immediately as it has probably been placed too deeply in the dermis. The rate and degree of subsidence of the implanted area is variable. Clinical experience has shown that overcorrection has been slow to resolve in the periorbital area and in treatment sites around the vermilion border of the lip. Thus, these areas should be treated cautiously and small amounts of CosmoDerm collagen implant should be implanted over several treatment sessions without overcorrection. Severely indurated lesions, which initially resist distention, often require several treatment sessions before desired correction is obtained. In such lesions it is preferable to implant within the scar rather than beneath it.

Needles may become occluded or dull during a treatment session and replacement may be necessary.

6. Gentle massage of the treated areas is recommended following implantation.
7. Additional implantations at intervals of two or more weeks may be required to achieve the desired level of correction.
8. The physician should instruct the patient to report to her/him any evidence of adverse texture change in the surrounding implantation site. Other problems

possibly associated with CosmoDerm collagen implant use should also be promptly brought to the attention of the physician.

9. Discard any unused material and the syringe after a single treatment visit.
10. For corrections in the glabellar region, CosmoDerm collagen implant is recommended over CosmoPlast collagen implant, because it is less likely to interrupt the local blood supply which could result in local necrosis.
11. Subsequent to device implantation saline is resorbed in less than 24 hours, which results in a rapid reduction in the magnitude of the overcorrection. Subsequently, a further, but more gradual (i.e., two or more weeks) reduction in the degree of overcorrection occurs as the implant stabilizes.

PATIENT INSTRUCTIONS:

It is recommended that the following information be shared with patients.

- To report an adverse reaction, phone the Product Support Department, INAMED Corporation, (800) 624-4261.
- Within the first 24 hours, patients should avoid:
 - Strenuous exercise
 - Extensive sun or heat exposure
 - Alcoholic beverages
 Exposure to any of the above may cause temporary redness, swelling, and/or itching at injection sites.
- Make-up may be applied a few hours post-treatment if no complications are present (e.g. open wounds, bleeding, and infection).

STORAGE:

CosmoDerm collagen implants should be stored at standard refrigerator temperatures (2-10°C / 36-50°F).

DO NOT FREEZE.

CosmoDerm collagen implants have a whitish, opaque or semi-opaque appearance. In the event that a syringe contains material that is clear (like water), do not use the syringe and notify INAMED Corporation immediately at (800) 624-4261.

STERILITY:

CosmoDerm human-based collagen implants are packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.

CAUTION:

Federal (USA) law restricts this device to sale by or on the order of a licensed physician, or an oral and maxillofacial surgeon.

INAMED Corporation
5540 Ekwill Street
Santa Barbara, CA 93111 USA
(800) 624-4261

Inamed
CosmoPlast™ Human-Based Collagen Implant

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION:

CosmoPlast collagen implant is a sterile device composed of highly purified human-based collagen that is crosslinked with glutaraldehyde, and dispersed in phosphate-buffered physiological saline containing 0.3% lidocaine.

CosmoPlast contains collagen purified from human fibroblast cell culture. The cell line used for collagen production is qualified by extensive testing for viruses, retroviruses, cell morphology, karyology, isoenzymes, and tumorigenicity. Prior to release each lot of human collagen is tested for protein concentration, purity, pH, lidocaine content, residue on ignition, differential scanning calorimetry, extrusion, appearance, sterility and pyrogenicity.

2. INTENDED USE / INDICATIONS

CosmoPlast collagen implant is injected into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars.

3. CONTRAINDICATIONS

- CosmoPlast collagen implant must not be used in patients with severe allergies manifested by a history of anaphylaxis.
- CosmoPlast collagen implant contains lidocaine and must not be used in patients with known lidocaine hypersensitivity.
- CosmoPlast collagen implant is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.

4. WARNINGS:

- CosmoPlast collagen implant must not be implanted into blood vessels. Avoid forceful injection into superficial dermal arterial branches of the face and scalp that could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Implantation of CosmoPlast collagen implant into dermal vessels may also cause vascular occlusion, infarction, or embolic phenomena, because collagen can initiate platelet aggregation.
- Local necrosis is a rare event, which has been observed following bovine collagen implantation. Most necroses reported through post-marketing surveillance of bovine dermal collagen have occurred after injection into the glabella.

- Some physicians have reported the occurrence of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis (PM), and dermatomyositis (DM) subsequent to bovine collagen injections in patients with no previous history of these disorders. Conflicting studies have been published in peer reviewed journals regarding the association between PM/DM and injectable bovine collagen. A causal relationship between bovine collagen injections and the onset of PM/DM, or the other connective tissue diseases listed, has not been established. The incidence and severity of such reactions after human collagen injections has not been determined.
- An increased incidence of cell-mediated and humoral immunity to various collagens has been found in systemic connective tissue diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, and progressive systemic sclerosis (scleroderma). Patients with these diseases may thus have an increased susceptibility to hypersensitivity responses and/or accelerated clearance of their implants when injected with bovine dermal collagen preparations. The incidence and severity of such reactions with human collagen injections has not been determined. Therefore, caution should be used when treating these patients.

5. PRECAUTIONS:

- CosmoPlast collagen implants are packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on experience with bovine collagen implants, the use of CosmoPlast collagen implant in an individual patient should be limited to 30 ml over a one-year period. The combination of CosmoDerm in conjunction with CosmoPlast collagen implant in an individual patient should be limited to 30 ml over a one-year period. The safety of injecting greater amounts on an annual basis has not been established.
- The safety of CosmoPlast use in patients with a known hypersensitivity to bovine collagen has not been studied.
- Injectable collagen should be used with caution in patients who are atopic or have a history of multiple allergies. Such patients may have a greater potential for exhibiting an allergic reaction.
- As with all transcutaneous procedures, CosmoPlast collagen implantation carries a risk of infection.
- Use of CosmoPlast collagen implant at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present, should be deferred until the underlying process has been controlled.
- The safety of CosmoPlast collagen implants for use during pregnancy or in infants and children has not been studied.

- CosmoPlast collagen implants should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs may, as with any injection, experience increased bruising or bleeding at injection sites.
- Based on experience with bovine collagen implants, CosmoPlast is not recommended for use in the periorbital area. Overcorrection of the vermilion border of the lip may be slow to resolve due to minimal tissue stresses at these sites. Therefore, caution is advised for CosmoPlast implant use in this area.
- The safety and effectiveness of CosmoPlast implantation for use in lip augmentation has not been established.

6. ADVERSE EVENTS

A. Human Collagen Implants

In a study to evaluate sensitization to CosmoDerm and CosmoPlast, 428 patients were injected intradermally with CosmoDerm 1 into the volar forearm and followed for 2 months. All reported adverse events with two or more occurrences in this study, are listed in Table 1 in descending order according to frequency.

Table 1 – Adverse Events with Two of More Occurrences in the Sensitization Study

Description of Adverse Event	Number	% Frequency
Cold Symptoms	17	4.1
Flu-Like Symptoms	8	2.0
Urinary Tract Infection	4	1.0
Bronchitis	3	0.7
Strep Throat	3	0.7
Sinus Infection	3	0.7
Acid Dyspepsia or Reflux	2	0.5
Back Ache, Pain, Spasm	2	0.5
Ear Infection	2	0.5
Fever and Slight Fever	2	0.5
High Blood Pressure	2	0.5
Insomnia	2	0.5
Sore Throat	2	0.5

Local Treatment Site Reactions

One subject reported redness and pain (moderate severity) at one week after the first injection. This was confirmed by the investigator as redness, tenderness, induration and swelling at the

injection site. These symptoms spontaneously resolved after 10 days without treatment or sequelae. The absence of an antibody response against CosmoDerm and histopathological examination of a biopsy of the injection site suggested that the injection site reaction was not immunologically-related to CosmoDerm injection.

B. Bovine Collagen Implants

The following adverse event information on Zyderm and Zyplast bovine collagen implants is based on a clinical study of 2800 Zyderm patients between 1979 and 1981, and 559 Zyplast patients between 1982 and 1986, as well as on post-market reports.

Sensitization reactions to injectable bovine collagen implants have occurred in 1-2% of treated patients, and have consisted of erythema, swelling, induration and/or urticaria at implantation sites. Often these reactions have occurred following an unrecognized or unreported positive bovine collagen skin test. Most of the remaining responses occurred in patients who became sensitized to Zyderm bovine collagen implant at some point during their course of treatment. Approximately 80% of these reactions occur within four weeks following the sensitizing dose.

Typically, allergic reactions to bovine collagen persist between one and nine months, with an average duration of four months. These reactions may be intermittent or continuous in nature. In rare instances, reactions have resolved in one or two weeks or have persisted for more than one year. Although several forms of therapy (antihistamines, NSAIDS, oral, topical and intralesional steroids) have been tried, they usually resulted in only temporary improvement. In most cases, time has proven to be the determining factor in the resolution of these reactions. In rare instances, patients have been left with residual firmness at the site of a resolved adverse reaction.

On rare occasions, the hypersensitivity response has progressed to a cystic reaction that may drain purulent material. The incidence and severity of this type of hypersensitivity response reported to date has been greater with Zyplast bovine collagen implant than with Zyderm bovine collagen implant. These reactions develop weeks to months following injection, may result in scar formation, and rarely require medical revision to correct. This type of reaction can occur as multiple and/or recurrent sterile abscesses, which tend to be persistent and resistant to drug therapy; careful incision and drainage has been a useful treatment.

The antigenic specificity of Zyplast bovine collagen implant has been determined to be identical to that of Zyderm bovine collagen implant. During clinical trials and post-marketing surveillance, the incidence of hypersensitivity responses to Zyplast collagen implant has been significantly lower than to Zyderm collagen implant; however, because of the potential for prolonged local availability of antigen, it is possible that the long-term rate of response to Zyplast collagen implant may exceed the low rate experienced to date.

Infections at implantation sites have occurred in less than one per thousand bovine collagen treated patients, and herpes simplex eruptions at sites that had been previously affected with herpes simplex, have been reported in less than one per ten thousand patients. These responses typically resolved quickly and without sequelae.

Systemic complaints have been reported by less than 0.5% of bovine collagen implant patients. During clinical testing and subsequent monitoring of patient complaints following exposure to Zyderm bovine collagen implant, a variety of systemic complaints has been reported. These reports have included flu-like symptoms (fever, myalgia, neuralgia, headache, nausea, malaise, or dizziness); pruritis; rash; transient visual disturbances including blurred vision; tingling and numbness; transient polyarthralgia; and various systemic diseases including immune-mediated diseases. Rare anaphylactoid responses have been reported with Zyderm bovine collagen implant, including acute episodes of hypotension, difficulty in breathing, tightness in chest, and/or shortness of breath.

As with any injection into the head or neck, the injected material may be inadvertently implanted in a blood vessel. Localized necrosis and/or sloughing, resulting in a scab and/or a scar, may occur following interruption of blood flow through blood vessel laceration or occlusion, or through tissue overdilatation that compromised vascularity. The extent of necrosis varies and follows the pattern of the tissue served by the vessel involved. This phenomenon has been reported more frequently in the glabellar region of the face than in other areas; nevertheless, the incidence with bovine dermal collagen is less than 1% of treated patients. Scar formation may also occur in conjunction with either infection and/or hypersensitivity responses. If implantation is followed by prolonged blanching or significant ecchymosis at the treatment site, gentle massage and close follow-up are recommended.

Forceful injection into superficial dermal arterial branches of the face and scalp could cause retrograde movement of the implant material into retinal arteries, resulting in vascular occlusion. Such a complication, although unlikely, has been reported with the use of Zyderm collagen implant in one patient, and resulted in the sudden and permanent loss of vision in one eye. Similar complications have been associated with other injectable preparations, including corticosteroids, local anesthetics, and angiographic agents. These findings emphasize the importance of avoiding implantation into blood vessels.

Local Treatment Site Reactions

Transient or minimal swelling, mild redness, and discomfort will probably occur at the implant site immediately following implantation. Increasing discomfort or swelling, or spreading redness should immediately be brought to the physician's attention.

Transient pain and tenderness at injection sites has been associated with the injection of collagen implants. On occasion, transient painless bruising or discoloration has been noted to develop at one or more of the implantation sites. Resolution has usually been spontaneous.

Less than 1% of patients receiving Zyderm bovine collagen implant have at some time reported an intermittent swelling response, involving moderate induration at the implant site and edema within the surrounding tissues. In some cases, these responses have been found to be associated with antibodies to bovine collagen. At times this has been accompanied by mild pruritis or minimal erythema, which may persist for a period up to several months. These reactions may last only a few hours and are usually associated with causes of peripheral vasodilatation, such as consumption of alcohol, prolonged exposure to sun and/or heat, exercise, and flare-ups of hay fever and other causes of nasal and sinus congestion. To date, these reactions have been self-limiting and have not been shown to adversely affect the long-term success of collagen implant correction; although, they may persist throughout the life of the implant.

Infections and reactivation of a pre-existing herpes simplex infection at collagen implant sites may occur in treated patients.

Approximately 20% of patients treated with Zyderm 2 bovine collagen implant have reported temporary palpable lumpiness or visible white patches at injection sites. Both of these types of treatment-associated responses resolved spontaneously without sequelae, and are believed to reflect the fact that with Zyderm 2 bovine collagen implant, a higher concentration of collagen can be injected in a single treatment session.

7. CLINICAL STUDIES:

A. Human Collagen Implants

Study Design:

A prospective, open label clinical study was conducted to evaluate patient immune system responses to CosmoDerm. Male and female subjects who were 18 years of age or older were enrolled. Exclusion criteria were: pregnant and/or nursing, treated with chemotherapy agents or corticosteroids within the past 3 months, allergic to lidocaine, or currently receiving treatment with immunosuppressive drugs. Patients were also excluded if they had a history of an autoimmune disorder, severe allergies manifested by a history of anaphylaxis, or a current disease state that could affect an immune response (e.g., flu, cancer, HIV).

A pre-treatment blood sample was taken followed by a 0.1 ml intradermal injection of CosmoDerm 1 into the volar forearm. The test site was monitored daily by the subject for signs of systemic and local reactions (e.g. erythema, pain, swelling). Each subject returned to the clinic at approximately 72 hours after the first CosmoDerm injection to have any observations recorded. After a 30-day observation period, subjects returned to the clinic for a second CosmoDerm injection, and the same procedures of test site observation by the subject and a 72-hour visit with the clinical staff took place. Thirty days after the second CosmoDerm injection, subjects returned for a final clinic visit, which included a post-treatment blood draw.

CosmoDerm Immune Response

Serum samples obtained before CosmoDerm exposure and 30 days after the second CosmoDerm injection were assessed with an ELISA capable of detecting IgG, IgM and IgA antibodies against Type I human collagen. No positive responses against human Type I collagen were observed. Equivocal titers (titers of 40-80), were found in four samples. Two of these four samples were from the same subject who displayed a pre-treatment titer of 40 and post-treatment titer of 80. Of the remaining two equivocal samples, one subject's sample (with a titer of 40) was pre-treatment, and a negative result was observed post-treatment. The other equivocal response (with a titer of 40) was from a post-treatment sample of a different subject. None of the equivocal response serum samples cross-reacted with bovine collagen.

B. Bovine Collagen Implants

Zyderm was studied in approximately 2800 patients with soft tissue contour deficiencies, most of which were treated between 1979 and 1981 by 400 investigators. While acne was treated in approximately 50% of the patients, a variety of soft tissue contour deficiencies were treated. Facial lesions accounted for approximately 95% of the soft tissue contour deficiencies. A

random sample of 95 patients was asked to provide a self assessment of the percent of correction at up to six months after their last treatment. Forty-seven patients responded and reported a median correction of 60-79%.

8. INDIVIDUALIZATION OF TREATMENT:

Severely indurated, sharply margined and very superficial lesions (e.g., ice-pick acne scars, viral pockmarks, and superficial rhytides such as some perioral lines) may be difficult to distend and, therefore, are difficult to correct. If a defect cannot be distended because of extensive scarring or non-elastic tissue, the course of correction will be prolonged, if correction is achievable.

Based on post-market studies with Zyderm bovine collagen, touch-up implantations at 6-18 month intervals may be required to maintain maximum correction. While areas with greater motion or mechanical stress (e.g. nasolabial folds), may require more frequent treatments, lesions such as acne scars may need touch-up injections less frequently. Nevertheless, if a stable level of correction is desired, all patients should be counseled to anticipate supplemental implantations.

9. HOW SUPPLIED

CosmoPlast collagen implant is supplied in individual treatment syringes with needles, and is packaged sterile for single patient use, ready for implantation.

To place an order, phone toll-free: (800) 624-4261

INSTRUCTIONS FOR USE:

1. Prior to treatment with CosmoPlast collagen implants, the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to maintain maximum correction.
2. A complete medical history should be obtained to determine whether the patient is an appropriate candidate for CosmoPlast collagen treatment.
3. The patient's soft tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pretreatment photographs are recommended.
4. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic.
5. CosmoPlast collagen implant is implanted through a fine-gauge needle. The needle should be placed into the plane(s) of apparent deformity and the defect should not be overcorrected. Best results with CosmoPlast collagen implant are achieved in defects requiring mid to deep dermal implant placement. The rate and degree of subsidence of correction in the implanted area is variable. Clinical experience has shown that overcorrection has been slow to resolve in the periorbital area and in treatment sites around the vermilion border of the lip. Therefore, caution is advised for CosmoPlast collagen implant use in these areas. Severely indurated lesions, which initially resist distention, may require several treatment sessions before

desired correction is obtained. In such lesions it is preferable to implant within the scar rather than beneath it.

Needles may become occluded or dull during a treatment session, and replacement may be necessary.

6. Vigorous massage of the treated areas is recommended following implantation.
7. Additional implantations at intervals of two or more weeks may be required to achieve the desired level of correction.
8. The physician should instruct the patient to report to her/him any evidence of adverse texture change in the surrounding implantation site. Other problems possibly associated with the use of CosmoPlast collagen implant should also be promptly brought to the attention of the physician.
9. Discard any unused material and the syringe after a single treatment visit.
10. For corrections in the glabellar region, CosmoDerm collagen implant is recommended over CosmoPlast collagen implant, because it is less likely to interrupt the local blood supply, which could result in local necrosis.

PATIENT INSTRUCTIONS:

It is recommended that the following information be shared with patients.

- To report an adverse reaction, phone the Product Support Department, INAMED Corporation, (800) 624-4261.
- Within the first 24 hours, patients should avoid:
 - Strenuous exercise
 - Extensive sun or heat exposure
 - Alcoholic beveragesExposure to any of the above may cause temporary redness, swelling, and/or itching at injection sites.
- Make-up may be applied a few hours post-treatment if no complications are present (e.g., open wounds, bleeding, and infection).

STORAGE:

CosmoPlast collagen implants should be stored at standard refrigerator temperatures (2-10°C / 36-50°F).

DO NOT FREEZE.

CosmoPlast collagen implants have a whitish, opaque or semi-opaque appearance. In the event that a syringe contains material that is clear (like water), do not use the syringe and notify INAMED Corporation immediately at (800) 624-4261.

STERILITY:

CosmoPlast human-based collagen implants are packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.

CAUTION:

Federal (USA) law restricts this device to sale by or on the order of a licensed physician, or an oral and maxillofacial surgeon.

INAMED Corporation
5540 Ekwill Street
Santa Barbara, CA 93111 USA
(800) 624-4261